American Journal of Hematology 60:231–236 (1999)

Anticoagulant-Induced Skin Necrosis in a Patient With Hereditary Deficiency of Protein S

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Skin necrosis is a rare but debilitating complication of treatment with vitamin K antagonist anticoagulants such as warfarin. A clinically similar syndrome has been reported less frequently with heparin therapy. We recently managed a thirty-year-old female patient who developed skin necrosis on her left lower extremity while on warfarin for postpartum DVT. The lesions started to develop 48 hr after stopping heparin therapy. Discontinuation of warfarin and reinstitution of heparin was complicated by a rapid decrease in platelet count consistent with heparin-induced thrombocytopenia (HIT) and its associated risk of platelet activation and thrombosis. The diagnosis was supported by the identification of antibodies against heparin/platelet factor 4 complexes in the patient's serum. The platelet count recovered and the patient improved after switching to therapy with the heparinoid danaparoid. Evaluation for a hypercoagulable state revealed a partial deficiency of protein S, a condition that previously was identified in two of her family members. It is not clear if this patient suffered from warfarin-induced skin necrosis, a manifestation of heparin-mediated platelet activation, or a complex condition in which both drugs contributed. HIT may affect 1–3% of patients who receive unfractionated heparin, and this case raises the possibility that heparin may contribute to, or cause, some episodes of skin necrosis attributed to warfarin. Because many patients who develop warfarin-induced skin necrosis have been treated initially with heparin, it would seem prudent to consider HIT in these situations. Am. J. Hematol. 60:231–236, 1999.

Key words: thrombocytopenia; thrombosis; skin necrosis; protein S deficiency; heparin; warfarin

INTRODUCTION

The anticoagulants warfarin and heparin are two of the most frequently prescribed drugs in clinical practice. While bleeding is the most common adverse effect of these medications, severe thrombotic complications have been associated with both warfarin and heparin therapy [1–5]. One such complication, skin necrosis, has been reported to affect 1:100 to 1:10,000 patients receiving warfarin and other vitamin K antagonists [1–3,5]. This condition arises between the third and tenth day of therapy, and typically involves skin overlying areas of fatty tissue such as the breast, thighs, and buttocks. A similar syndrome has been reported more rarely with heparin therapy [4,6]. Necrosis usually develops at sites of subcutaneous heparin injection, but has been reported after intravenous administration [6–8]. Heparin-related skin necrosis is a manifestation of a common complication of heparin therapy, heparin-induced thrombocytopenia (HIT) [4,6]. Once thought to be an isolated decrease in platelet count that resolves with discontinuation of the drug, HIT appears to be an antibody-mediated intensely prothrombotic condition associated with platelet activation and increased thrombin production [9,10]. Immune-mediated HIT may affect 1–3% of patients receiving unfractionated heparin, and some studies have reported up to 50% of patients developing thrombotic complications over the weeks following the diagnosis of HIT [4]. Given that HIT is a fairly common side effect of heparin, and

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Received for publication 15 April 1998; Accepted 4 November 1998

that most patients with warfarin-induced skin necrosis have received initial treatment with heparin therapy, it is conceivable that heparin-mediated platelet activation could contribute to warfarin-related necrosis or even cause necrosis that might mistakenly be attributed to warfarin. In this report we describe a patient with hereditary protein S deficiency who developed typical lesions of warfarin-induced skin necrosis during treatment for postpartum deep vein thrombosis (DVT). She had received heparin as initial therapy. Upon switching back to heparin, a rapid decrease in platelet count occurred, raising the possibility that her skin lesions were caused by HIT, or possibly a complex process in which both warfarin and heparin were contributing.

METHODS

The heparinoid danaparoid (Orgaran®, formerly Org 10172 manufactured by N.V. Organon, Oss, The Netherlands) was administered as a 2,500-unit IV bolus, followed by 400 units/hr for 4 hr, 300 units/hr for 4 hr, and then 200 units/hr by continuous IV infusion for the remainder of therapy [11]. Effectiveness of anticoagulation was determined using a Chromogenic substrate-based low molecular weight heparin (LMWH) assay from Diagnostica Stago (Asnieres-sur-Seine, France) on an STA coagulation analyzer (Diagnostica Stago) according to the manufacturer's instructions. The desired therapeutic range for danaparoid was 0.5 to 0.8 anti-factor Xa units/ml plasma as described by Magnani [11]. Platelet aggregometry for HIT was performed at the Mayo Clinic, Rochester, MN. An enzyme-linked immunosorbent assay for heparin/platelet factor 4 antibodies (Asserachrom HPIA) was obtained from Diagnostica Stago, and performed according to the manufacturer's specifications.

CASE PRESENTATION

A thirty-year-old woman developed a left lower extremity DVT 12 days after delivery of her third child by Cesarean section. Doppler-ultrasound studies revealed clot extending from the iliac to the popliteal vein. She had no prior history of thrombotic problems and had no other medical conditions. Her family history was notable for two cousins with thromboses associated with protein S deficiency. The patient was initially treated with unfractionated heparin to maintain an activated partial thromboplastin time (aPTT) of two times normal control and was started on warfarin on day 2 of hospitalization, reaching a therapeutic international normalized ratio (INR) (3.2) on day 5. The platelet count prior to starting heparin therapy was 335,000/mm^3. No additional platelet counts were obtained during the hospitalization. The overlap period between heparin and warfarin was 5 days and she was discharged on day 7 on 4 mg of warfarin per day. Twenty-four hr after discharge, areas of dark discoloration developed on the left thigh. The next morning, numerous large painful blood-filled blisters were present on the left thigh and calf and she returned to the hospital. The patient's temperature was 102.6°F. The left leg was markedly swollen to the level of the groin and warm to touch. The anterior, medial, and posterior aspect of the left thigh had several hemorrhagic bullae, the largest measuring 10 × 15 cm, and a similar large lesion was noted on the left calf. The bullae were surrounded by areas of intense erythema. An area of necrosis with eschar 2 cm in diameter was present on the dorsum of the left foot. Distal pulses were intact in both legs and no other skin lesions were noted on other parts of the body. A venogram demonstrated persistence of clot in the left leg extending from the popliteal to the common iliac vein and included the deep femoral system. It was felt that this probably represented the patient's original postpartum clot; however, recent extension could not be ruled out as a venogram had not been done during her first hospitalization. The blood coagulation parameters are listed under day 1 in Table I. The initial diagnosis was warfarin-induced skin necrosis and the patient was treated with fresh frozen plasma, vitamin K, and a continuous infusion of unfractionated heparin. She also received infusions of urokinase directly into the femoral artery and vein on the left side in an attempt to dissolve the venous clot from both the distal and proximal ends. This treatment resulted in partial restoration of venous flow. Over the following 48 hr, the skin lesions and swelling in the left leg did not progress; however, a marked decrease in platelet count was observed, raising the possibility of HIT (Table I and Fig. 1). Heparin was discontinued, a continuous infusion of urokinase was started, and the patient was transferred to a tertiary care center.

Upon arrival at the tertiary care facility, a Doppler-

TABLE I. Coagulation Parameters During Hospitalization for Skin Necrosis*

Day	Platelets	PT	aPTT	Fibrinogen	FDP	Heparinoid[a]
1	604,000	42	55	435	5–20	—
2	138,000	—	—	—	—	—
3	79,000	16.2	54	254[b]	>20[b]	—
4	114,000	15.6	52	—	—	—
5	210,000	14.7	44	—	—	0.67
6	300,000	13.7	27	—	—	0.56
7	415,000	13.3	27	—	—	0.66
8	485,000	14.0	25	—	—	0.8
9	558,000	—	—	—	—	0.65
10	676,000	—	—	—	—	—

*PT, prothrombin time; aPTT, activated partial thromboplastin time; FDP, fibrin degradation products.
[a]The heparinoid level is measured in anti-factor Xa units per ml of plasma.
[b]The patient was receiving intravenous urokinase during these measurements.

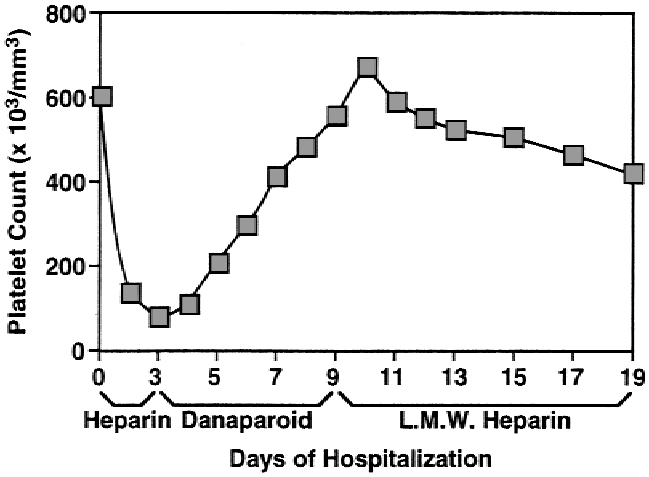

Fig. 1. Platelet count in relationship to anticoagulant therapy for the patient's hospitalization for skin necrosis. Doses of anticoagulants are described in the Methods and Case Presentation sections.

ultrasound study demonstrated complete obstruction of the femoral venous system on the left. The urokinase infusion was discontinued and therapy with danaparoid was initiated as described in the methods section. Intravenous immunoglobulin (IgG), 1 gm/kg/day was administered for 2 days based on anecdotal evidence that this therapy has some efficacy in immune-mediated HIT [12,13]. Results of a platelet aggregation based assay for HIT performed on serum drawn on day 1 of her second hospitalization showed slight platelet aggregation that was considered equivocal for HIT. On day 5, the plastic surgery service unroofed and debrided the lesions and instituted treatment with silver sulfadiazine (silvadene) cream and dressing changes. The platelet count, which reached a nadir on day 3, corrected during danaparoid therapy (Fig. 1), and over the subsequent week swelling in the left leg improved and the erythema surrounding the bullous lesions resolved. Because of difficulties with availability of danaparoid, the patient was switched to the LMWH enoxaparin (Lovenox, Rhone-Poulenc Roher, Collegeville, PA) 1 mg/kg SQ every 12 hr on day 9. Over the subsequent 6 months, the patient has maintained a normal platelet count on LMWH, blood flow has improved in the left femoral venous system, and the skin lesions are slowly healing. After her discharge, plasma samples from days 4 and 7 of her second hospitalization were tested for the presence of the anti-heparin/platelet factor 4 antibodies commonly found in patients with HIT, and both samples were found to be strongly positive. An evaluation for a hypercoagulable state performed 10 weeks after discharge revealed a free protein S activity of 18% of normal and a free protein S antigen level of 14% of normal (normal range 55–120% for both activity and antigen assays). Antithrombin III and protein C levels were normal (77% and 103% of normal, respectively) and tests for activated protein C resistance, lupus anticoagulant, and anticardiolipin antibodies were negative.

DISCUSSION

The patient described in this report appeared to have sustained a typical postpartum deep vein thrombus with a possible contribution, in retrospect, from protein S deficiency. Her initial hospitalization was uneventful; however, shortly after discharge, signs consistent with warfarin-induced skin necrosis developed. Skin necrosis is a serious, but fortunately rare, complication of warfarin therapy typically involving skin overlying fatty tissue in the breast, buttocks, and thighs [1–3,5]. Symptoms of pain, cold, or pressure in the involved areas develop between days 3 and 10 of therapy and progress within hours to a few days to hemorrhagic bullae with underlying necrosis and eschar formation. Histologic examination demonstrates occlusion of small veins, venules, and capillaries in the dermis and subcutaneous tissues [14]. The process may be triggered by a transient hypercoagulable state due to a rapid decrease in protein C at the start of warfarin therapy, prior to therapeutic decreases in factors II, IX, and X [2,3,5,15,16]. This is due to the shorter half-life of protein C (6–10 hr) compared with the other proteins (20–24 hr for factor IX to 2–5 days for prothrombin). Consistent with this hypothesis are reports of warfarin-induced skin necrosis in patients with hereditary deficiency of protein C. Lower basal levels of protein C could exacerbate the effect produced by warfarin, and in one study, 5 of 16 patients with warfarin-induced skin necrosis had protein C deficiency [17]. Our patient has a deficiency of protein S, a cofactor required by protein C for maximal anticoagulant activity. Protein S levels decrease during warfarin therapy but usually not to the same degree as protein C, which may explain why protein S deficiency is rarely associated with warfarin-induced skin necrosis [18–22]. Despite these observations, it is important to note that the majority of patients with warfarin-induced skin necrosis do not have an identifiable inherited hypercoagulable state and, in those who do, it is not certain that a causal relationship exists [2,5,23].

While warfarin-induced skin necrosis has been reported in a number of clinical settings, several reviews have identified features common to most cases. More than 80% of patients are woman and the majority are acutely ill and hospitalized, with DVT or pulmonary embolism the predominant indications for initiating anticoagulation [1–3,5]. Skin necrosis associated with warfarin use rarely occurs in an ambulatory setting, such as in patients with new onset atrial fibrillation [2]. It would appear, therefore, that the presence of an acute proco-

agulant process such as a thrombus is required. Early reports suggested that large loading doses of warfarin (>10 mg) resulted in severe reduction of factor VII (and presumably protein C) and were, therefore, more likely to induce the syndrome; however, there is no clear relationship between initial intensity of treatment and skin necrosis [2,24]. Another potential procoagulant stimulus these patients may be exposed to is heparin. While not directly addressed by published studies, the majority of reported patients with warfarin-induced skin necrosis appear to have received heparin as initial treatment for their clot. There is a single report of skin necrosis occurring during concurrent warfarin and heparin therapy [22], so it would appear that necrosis usually follows the termination of therapy with heparin. It is not clear if thrombocytopenia consistent with HIT was noted in any patient with warfarin-induced skin necrosis during or after cessation of heparin therapy. Heparin was not initially suspected as a contributor to our patient's skin necrosis because her platelet count was elevated on admission, and the single platelet count measured during her earlier hospitalization for DVT was before the initiation of heparin therapy. Upon reinstitution of heparin, however, the dramatic abrupt drop in platelet count brought the syndrome of HIT to the forefront.

HIT, which may affect 1–3% of patients who receive unfractionated heparin, is characterized by a decrease in platelet count to <150,000/mm^3 or a >50% decrease in platelet count from baseline [9]. Thrombocytopenia usually occurs 5–10 days after starting therapy; however, as with our patient, it may occur rapidly (within hours) if there has been prior exposure to heparin. Recent studies indicate that HIT is an immune-mediated disorder arising as a result of antibodies to heparin in complex with certain proteins, usually platelet factor 4 [9,25]. The immune complexes occupy Fc receptors on platelets resulting in platelet activation, the release of platelet microparticles, and increased thrombin production [5,9]. Up to 50% of patients may develop a thrombotic event in the weeks following an episode of immune-mediated HIT, often after discharge from the hospital when they are no longer on heparin [4]. Diagnosis is aided by the demonstration of antibodies to heparin/protein complexes by platelet based serotonin release assay, platelet aggregation assay, or enzyme-linked immunosorbant assay [9]. Heparin-induced skin necrosis, first described in 1973, is now thought to be caused by an immune mechanism identical to the one in classic HIT, although not all patients with skin necrosis have thrombocytopenia [3–6]. Necrosis occurs at sites of subcutaneous heparin injection or in skin overlying fatty tissues when administered IV [6–8].

Heparin should be discontinued immediately when HIT develops and the need for further anticoagulation reassessed. In our patient, restarting warfarin was not considered an option because of the strong likelihood that it contributed to her skin necrosis. In addition, Warkentin and colleagues reported recently that initiation of warfarin after stopping heparin in HIT is associated with a syndrome of venous limb gangrene [26,27]. In contrast to warfarin-induced skin necrosis, the venous limb gangrene syndrome is characterized by distal ischemic necrosis of the limb in association with DVT. The mechanism underlying this condition may involve a warfarin-induced decrease in protein C concentration to levels inadequate to cope with the enhanced thrombin generation caused by HIT. While it is reasonable to hypothesize that congenital deficiency of protein C or protein S could exacerbate this situation, these abnormalities were not identified in the original venous limb gangrene patients described by Warkentin, and only one of these patients experienced skin necrosis with a distribution typical of classic warfarin-induced necrosis [26]. Venous limb gangrene, therefore, appears to be distinct from classic warfarin-induced skin necrosis. Although the processes responsible for the different presentations of these two complications of warfarin therapy are not clear, the available data suggests that congenital deficiencies of regulatory proteins such as protein C and protein S may be more important to the development of the proximal necrosis seen in warfarin-induced skin necrosis than to the distal necrosis that occurs in the venous limb gangrene syndrome. Protein S deficiency in our patient, therefore, may have predisposed her to skin necrosis. Furthermore, venous limb gangrene does not appear to occur when warfarin is started while the patient is still receiving heparin, as was the case in our patient.

The use of LMWH in HIT is controversial and has been discouraged by several authors [4,5,9]. While LMWH has been used successfully in HIT [28], there is virtually 100% in vitro cross-reactivity between the anti-heparin/platelet factor 4 antibodies found in HIT and LMWH, and some patients will not improve or will progress on this therapy [9]. Substantial experience has been compiled with the heparinoid danaparoid, a mixture of low molecular weight glycosaminoglycans, predominantly heparan sulfate and dermatan sulfate [29]. This preparation has now been used in more than 600 patients with HIT, with >90% showing improvement [11]. Danaparoid has relatively low cross-reactivity with HIT antibodies in in vitro tests (10–20%) and the risk of in vivo cross reactivity appears to be <5% [9,11]. The direct thrombin inhibitor recombinant hirudin has now been approved for use in the United States for the treatment of HIT, and is a reasonable alternative to danaparoid [30]. Another small molecule thrombin inhibitor efficacious in HIT, Argatroban, should receive approval in the near future [31].

The cause of the skin necrosis in our patient is not clear and, indeed, she may well be the victim of several

pathologic processes simultaneously contributing to a hypercoagulable condition. The clinical findings at the time of her second hospitalization were consistent with warfarin-induced skin necrosis. Some atypical features were present, such as the skin lesions being confined to one limb and necrosis extending to the calf and foot; however, these findings have been observed in some patients with the diagnosis of warfarin-induced skin necrosis [18,32]. As there are case reports linking protein S deficiency to this disorder, the subsequent identification of a low protein S level in the patient supported the diagnosis. It was only after reinstitution of therapy with heparin, and the subsequent impressive drop in platelet count, that the possibility that heparin was contributing to the necrosis was considered. This event suggested a more complex scenario in which skin necrosis could have been due to warfarin exacerbated by platelet activation and increased thrombin production triggered by the heparin used to initially treat her venous thrombus, or an atypical presentation of HIT aggravated by warfarin therapy. In either case, the possibility of HIT required that heparin be discontinued despite the presence of a venous thrombus and skin necrosis. Considering that HIT may be a relatively common occurrence (1–3% of patients) during therapy with unfractionated heparin, this case suggests that heparin-mediated platelet activation is likely to contribute to some cases of warfarin-induced skin necrosis. Indeed, skin necrosis caused by HIT may be diagnosed mistakenly as warfarin-induced necrosis. Therefore, it would seem prudent to test for HIT in patients with the diagnosis of warfarin-induced skin necrosis.

ACKNOWLEDGMENTS

The authors thank Ms. Patricia Baxter, Supervisor of the coagulation laboratory at Vanderbilt University Hospital, for her technical assistance in this case. We are also grateful to Dr. John M. Flexner for helpful commentary during the course of writing this manuscript.

REFERENCES

1. Cole MS, Minifee PK, Wolma FJ. Coumarin necrosis—a review of the literature. Surgery 1988;103:271–277.
2. Eby CS. Warfarin-induced skin necrosis. Hematol-Oncol Clin N Am 1993;7:1291–1301.
3. Griffin JP. Anticoagulants and skin necrosis. Adverse Drug React Toxicol Rev 1994;13:157–167.
4. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med 1996;101:502–507.
5. Sallah S, Thomas DP, Roberts HR. Warfarin and heparin-induced skin necrosis and the purple toe syndrome: infrequent complications of anticoagulant treatment. Thromb Haemost 1997;78:785–790.
6. Warkentin TE. Heparin-induced skin lesions. Br J Haematol 1996;92: 494–497.
7. Kelly RA, Gelfand JA, Pincus SH. Cutaneous necrosis caused by systemically administered heparin. J Am Med Assoc 1981;246:1582.
8. Rongioletti F, Pisani M, Ciaccio M, Rebora A. Skin necrosis due to intravenous heparin. Dermatologica 1989;178:47–50.
9. Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards a consensus. Thromb Haemost 1998;79:1–7.
10. Chong BH, Pitney WR, Castaldi PA. Heparin-induced thrombocytopenia: association of thrombotic complications with heparin-dependent IgG antibody that induces thromboxane synthesis and platelet aggregation. Lancet 1982;2:1246–1249.
11. Magnani HN. Heparin-induced thrombocytopenia (HIT): an overview of 230 patients treated with orgaran (org 10172). Thromb Haemost 1993;70:554–561.
12. Harenberg J, Huhle G, Piazolo L, Wang LU, Heene DL. Anticoagulation in patients with heparin-induced thrombocytopenia type II. Semin Thromb Hemost 1997;23:189–196.
13. Frame JN, Mulvey KP, Phares JC, Anderson MJ. Correction of severe heparin-associated thrombocytopenia with intravenous immunoglobulin. Ann Intern Med 1989;111:946–947.
14. Faraci PA, Deterling RA, Steing AM, Rheinlander HF, Cleveland RJ. Warfarin-induced necrosis of the skin. Surg Gynecol Obstet 1978;146: 695–700.
15. Vigano S, Mannuci PM, Solinas S, Botosso B, Mariani G. Decrease in protein C antigen and formation of an abnormal protein soon after starting oral anticoagulant therapy. Br J Haematol 1984;57:213–217.
16. Vignano-D'Angelo S, Comp PC, Esmond CT, D'Angelo A. Relationship between protein C antigen and anticoagulant activity during oral anticoagulation and in selected disease states. J Clin Invest 1986;77: 416–425.
17. Broekmans AW, Bertina RM, Loeliger EA, Hofmann V, Klingemann HG. Protein C and the development of skin necrosis during anticoagulant therapy [letter]. Thromb Haemost 1983;49:251.
18. Grimaudo V, Gueissaz F, Hauert J, Sarraj A, Kruithof EKO, Bachmann F. Necrosis of skin induced by coumarin in a patient deficient in protein S. Br Med J 1989;298:233–234.
19. Proby CM, Chitolie A, Bevan DH, Mortimer PS. Cutaneous necrosis associated with protein S deficiency. J Royal Soc Med 1990;83:646–647.
20. Goldberg SL, Orthner CL, Yalisove BL, Elgart ML, Kessler CM. Skin necrosis following prolonged administration of coumarin in a patient with inherited protein S deficiency. Am J Hematol 1991;38:64–66.
21. Anderson DR, Brill-Edwards P, Walker I. Warfarin-induced skin necrosis in 2 patients with protein S deficiency: successful reinstatement of warfarin therapy. Haemostasis 1992;22:124–128.
22. Berkompas DC. Coumarin skin necrosis in a patient with a free protein S deficiency. Indiana Med 1991;81:788–791.
23. Comp PC, Elrod JP, Karzenski S. Warfarin-induced skin necrosis. Semin Thromb Hemost 1990;16:293–298.
24. van Amstel WJ, Boekhout-Mussert MJ, Loeliger EA. Successful prevention of skin necrosis by timely administration of vitamin K. Blut 1978;36:89–93.
25. Amiral J, Bridey F, Wolf M, Boyer-Neumann C, Fressinaud E, Vissac AM, Peynaud-Debayle E, Dreyfus M, Meyer D. Antibodies to macromolecular platelet factor 4-heparin complexes in heparin-induced thrombocytopenia: a study of 44 cases. Thromb Haemost 1995;73:21–28.
26. Warkentin TE, Elavathil LJ, Hayward CPM, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. Ann Intern Med 1997;127:804–812.
27. Warkentin TE. Heparin-induced thrombocytopenia: IgG-mediated platelet activation, platelet microparticle generation, and altered procoagulant/anticoagulant balance in the pathogenesis of thrombosis and venous limb gangrene complicating heparin-induced thrombocytopenia. Transfus Med Rev 1996;10:249–258.

28. Harenberg J, Huhle G, Piazolo L, Wang LU, Heene DL. Anticoagulation in patients with heparin-induced thrombocytopenia type II. Semin Thromb Hemost 1997;23:189–196.
29. Bradbrook ID, Magnani HN, Moelker HCT, Morrison PJ, Robinson J, Rogers HJ, Spector RG, Van Dinther T, Wijnand: ORG 10172: a low molecular weight heparinoid anticoagulant with a long half-life in man. Br J Clin Pharmacol 1987;23:667–675.
30. Schiele F, Vuillement A, Kramarz P, Kieffer Y, Anguenot T, Bernard Y, Bassand JP. Use of recombinant hirudin as antithrombotic treatment in patients with heparin-induced thrombocytopenia. Am J Hematol 1995;50:20–25.
31. Matsuo T, Kario K, Chikahira Y, Nakao K, Yamada T. Treatment of heparin induced thrombocytopenia by use of argatroban, a synthetic thrombin inhibitor. Br J Haematol 1992;82:627–629.
32. Haimovici H, Bergan JJ. Coumadin-induced skin necrosis versus venous gangrene of the extremities. J Vasc Surg 1987;5:655–656.